REMARKS

Claims 1, 5, 7, 9, 13, 39, 40, and 42 have been amended and new claim 48 has been added. Claims 1-5, 7-13, 39-43, and 48 are pending in the instant application. Support for the amendments to the claims can be found in the specification at, for example, page 2, lines 13 and 15-16; page 4, lines 22-28; page 38, line 29 to page 39, line 6; page 71, lines 23-26; Table I (pages 15-16); and Figures 1 and 2A-2B. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

Applicants note first that the claims have been amended to recite nucleic acid molecules encoding murine and human FGF-like polypeptides and murine and human FGF-like polypeptide variants. As discussed in Applicants' response to the Office Action mailed September 26, 2001, Examiner Nguyen indicated in a telephone interview with Applicants' representative Kevin Noonan on April 5, 2002 that the as-filed specification did, in fact, assert a specific, substantial, and credible utility for murine FGF-like molecules. Although Applicants, in their response, respectfully disagreed with the assertion that the as-filed specification did not also assert a specific, substantial, and credible utility for human FGF-like molecules, Applicants amended the claims as suggested by the Examiner – and *solely* in an effort to expedite prosecution of the instant application – to recite only murine FGF-like nucleic acid molecules. Applicants, however, stated in their response that the amendments did not constitute an admission that the human FGF-like molecules lack utility or that the instant specification does not assert a specific, substantial, and credible utility for the human FGF-like molecules. In view of the Examiner's decision to maintain the rejection under 35 U.S.C. § 101 despite Applicants' amendment of the claims pursuant to the Examiner's suggestion, Applicants have amended the claims to again recite nucleic acid molecules encoding human FGF-like polypeptide and human FGF-like polypeptide variants.

1. New Claim 48

Applicants wish to direct the Examiner's attention to new claim 48, which recites an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 2; wherein the aspartic acid residue at position 2 may be substituted with a glutamic acid residue; the threonine residue at position 6 may be

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substituted with a serine residue; the valine residue at position 17 may be substituted with a leucine residue; the glutamine residue at position 75 may be substituted with an arginine residue; the glutamine residue at position 82 may be substituted with a glutamic acid residue; the threonine residue at position 98 may be substituted with an alanine residue; the arginine residue at position 105 may be substituted with a glutamine residue; the histidine residue at position 145 may be substituted with an arginine residue; the histidine residue at position 153 may be substituted with an asparagine residue; the arginine residue at position 154 may be substituted with a glutamine residue; the alanine residue at position 157 may be substituted with a threonine residue; the leucine residue at position 167 may be substituted with a methionine residue; the glutamic acid residue at position 176 may be substituted with an aspartic acid residue; the glutamine residue at position 184 may be substituted with a glutamic acid residue; the residue at any of positions 3-5, 7-10, 11, 16, 20, 21, 25, 26, 29, 54, 56, 70, 74, 114, 148-150, 156, 158, 159, 162, 171-173, 175, 177, 178, 180, 182, 198, or 200 may be substituted with any naturally occurring amino acid residue; and wherein expression of the polypeptide in a transgenic animal results in either a decrease in the animal's body weight, a decrease in animal's liver or spleen weight as a percentage of the animal's body weight, or an increase in the animal's thymus weight as a percentage of the animal's body weight; or a nucleotide sequence that is complementary to the above nucleotide sequence. Applicants contend that new claim 48 embraces *only* nucleic acid molecules encoding conservatively-substituted variants of the amino acid sequence of SEQ ID NO: 2.

In addition, Applicants note that claim 1, as originally filed, recited, in part, an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide that is at least about 80 percent identical to the polypeptide set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or a nucleotide sequence encoding a polypeptide that has a substitution or deletion of 1 to 100 amino acid residues as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4. Applicants also note that claim 1 was *only* assigned to group I in the Restriction Requirement mailed January 27, 2000. Applicants contend that because the genus of human FGF-like polypeptide variants recited in originally filed claim 1, and assigned to the invention of group I in the Restriction Requirement mailed January 27, 2000, encompasses each and every member of the genus of human FGF-like polypeptide variants recited in new claim 48, restriction of new claim 48 would be improper.

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2. Rejection of claims 1-5, 7-13, and 39-43 under 35 U.S.C. § 101

The Office Action asserts a rejection of claims 1-5, 7-13, and 39-43 under 35 U.S.C. § 101 as being directed to an invention having no apparent or disclosed specific, substantial, and credible utility. The Action states that the specification does not disclose the specific biological function or significance of the polypeptides encoded by the claimed nucleic acid molecules. The Action also states that since it is well-recognized in the art that the members of the FGF family possess a broad range of biological activities involving cell growth and differentiation, a skilled artisan could not predict which biological activity the disclosed polypeptides possess *solely* on the basis of structural similarity to the FGF family. The Action also states that each of the utilities contemplated by the as-filed specification constitutes a "non-specific utility" requiring additional knowledge about the specific biological function of the polypeptides encoded by the claimed nucleic acid molecules (*e.g.*, a specific receptor that the polypeptides interact with or a well-established biological pathway in which the polypeptides play a role) before the claimed nucleic acid molecules could be regarded as having a specific purpose or conferring a real world benefit. In addition, the Action states that the assertion that the claimed nucleic acid molecules could be used to *make* a transgenic mouse does not constitute a specific, substantial, and credible utility. Applicants traverse this rejection.

Applicants respectfully disagree with the Action's assertion that the asserted utility of the claimed FGF-like nucleic acid molecules is based *solely* on the structural similarity of the disclosed FGF-like polypeptides to members of the FGF family. On the contrary, the instant application discloses an explicit example of a biological function for the protein product of the claimed nucleic acid. Specifically, the instant application discloses that 6-8 week old transgenic mice that overexpressed an FGF-like transgene exhibited an abnormal phenotype generally characterized as inhibited or delayed maturation, including reduced body weight, reduced liver weight as a percent of body weight, reduced spleen weight as percent of body weight, increased thymic weight as percent of body weight, and poorly developed ovaries with lack of significant follicular development (page 4, lines 22-28). This was *not* a prophetic example, and was *not* a speculative function or utility. Rather, this disclosure provided a phenotype associated with overexpression of the claimed nucleic acid. It was also *not* based *solely* on structural similarity. Based on this biological evidence, Applicants contend that the asserted utility of the claimed polypeptides rests on *more* than their structural similarity to members of the FGF family.

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Applicants also respectfully disagree with the Action's assertion that the asserted utility for the claimed FGF-like polypeptides is making a transgenic mouse that expresses an FGF-like transgene. Applicants provided an art-recognized example of determining a phenotype associated with a novel nucleic acid: showing the effect of overexpressing the nucleic acid in a cell or animal and detecting the effect. This, not the mere creation of a transgenic mouse, was the intent and effect of the cited disclosure, as would be recognized by one having ordinary skill in the art.

Applicants also respectfully disagree with the Action's assertion that to satisfy the requirements of 35 U.S.C. § 101, Applicants have the burden of establishing that the as-filed specification describes the *specific biological function* of the FGF-like polypeptides encoded by the claimed nucleic acid molecules. Applicants contend, instead, that the appropriate test for determining whether the claimed invention has patentable utility is provided by the *Utility Examination Guidelines*, which state that to satisfy the utility requirements of 35 U.S.C. §§ 101 and 112, first paragraph, Applicants' disclosure must contain an assertion of a specific and substantial utility that is credible. *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1098 (2001).

Applicants first address whether the instant application contains an assertion of a *specific* utility. The *Revised Interim Utility Guidelines Training Materials* ("*Training Materials*") define "specific utility" as utility that is *specific* to the subject matter claimed, as contrasted with a *general* utility that would be applicable to the broad class of the invention. *Training Materials*, at p. 5 (1999) <http://www.uspto.gov/web/menu/utility.pdf>. To illustrate the difference between a specific utility and a general utility, the *Training Materials* describe a claim reciting a polynucleotide for which the only disclosed use is as a gene probe or chromosome marker. Since all polynucleotides could be used as gene probes or chromosome markers, such a use would not constitute a specific utility. Applying these principles to the instant application, it is clear that the broad class of the invention is nucleic acid molecules, while the claimed invention encompasses particular nucleic acid molecules encoding murine and human FGF-like polypeptides and FGF-like polypeptide variants.

Additionally, with regard to whether the instant application contains an assertion of a specific utility, Applicants note that the instant application teaches that FGF-like mRNA expression is found primarily in the liver (page 4, line 39 to page 5, line 1; page 80, lines 14-16; and page 81, lines 2-5), the structural similarity of FGF-like polypeptide to members of the FGF family (Figures 3A-3D), and the likelihood that FGF-like polypeptide is secreted into the bloodstream where it may exert effects

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on distal sites (page 5, lines 5-7; page 77, line 27 to page 78, line 1; and page 79, lines 22-25). In view of this disclosure of experimental results obtained for the claimed nucleic acids, Applicants specifically assert that the FGF-like molecules of the present invention may be useful for, *inter alia*, regulating cells within or near the liver or regulating intestinal cell activity (page 2, lines 20-21; page 2, line 29 to page 3, line 1; page 3, lines 8-9 and lines 26-28; and page 5, lines 7-9). More importantly, the instant application further teaches a specific phenotype expressed by transgenic mice expressing an FGF-like transgene of the invention (page 4, lines 22-28). Specifically, transgenic mice expressing an FGF-like transgene exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, including reduced body weight, reduced liver weight as a percent of body weight, reduced spleen weight as percent of body weight, increased thymic weight as percent of body weight, and poorly developed ovaries with lack of significant follicular development. Applicants contend that a skilled artisan would recognize, in view of this explicit disclosure, that polypeptides encoded by the claimed sequences could be useful, for example, as growth or fat deposition inhibitors (page 5, lines 15-16) or in the treatment or prevention of liver-related diseases and disorders (page 5, lines 23-25 and page 76, lines 4-5). Moreover, Applicants contend that because not *all* nucleic acid molecules encode polypeptides that are expressed primarily in the liver, share structural similarity with members of the FGF family, are secreted into the bloodstream, or produce the inhibited or delayed maturation phenotype described above when overexpressed in an animal, and that their claims do not encompass *all* nucleic acid molecules, the asserted utility is a *specific* utility.

Applicants next address whether the instant application contains an assertion of a *substantial* utility. The *Training Materials* define "substantial utility" as utility having a "real world" use. *Training Materials*, at p. 6 (1999). Applicants contend that since members of the FGF family have substantial real world use, for example, as regulators of cell proliferation, differentiation, and function (Galzie *et al.*, 1997, *Biochem. Cell Biol.* 75:669-85), and in view of the teachings of the instant specification described above, the claimed polypeptides would have substantial real world use as, for example, regulators of liver cell growth. In addition, the asserted uses are substantial because they have "real world" effects, *inter alia*, causing reduced body weight.

The Action asserts that the issue of utility presented by the instant application is directly analogous to the issue of utility addressed in *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA)

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689 (1966). In *Brenner*, the Supreme Court determined that a chemical *process* (*not* the chemicals themselves) for producing steroids belonging to a class of steroids, said class of steroids comprising one known member previously proven effective in inhibiting tumors in mice, lacked patentable utility because the applicants had not disclosed a sufficient likelihood that the steroids produced by the claimed process had similar tumor-inhibiting properties. Applicants respectfully disagree with the Action's assertion that the issue of utility presented by the instant application is *directly* analogous to the issue of utility addressed in *Brenner*. As stated in *Brenner*, those applicants disclosed nothing more than (a) a process for producing steroids, and (b) that the compounds produced by the claimed process were homologues of a known compound shown to have tumor-inhibiting properties. In stark contrast, the instant application affirmatively teaches specific nucleic acid molecules encoding polypeptides that were found to be actually *expressed* in animals, primarily in the liver. Further, overexpression of these polypeptides in transgenic mice produces an inhibited or delayed maturation phenotype, including, for example, reduced body weight and reduced liver weight as a percent of body weight. Applicants contend, therefore, that the instant application provides the public with a specific benefit (*i.e.*, a particular member of the FGF family, and the first FGF shown to be expressed primarily in the liver, and one associated with a specific function). This situation is wholly unlike the circumstances in *Brenner*, where the chemical process of *Brenner* produced a class of compounds which might not have been produced in nature and which might have had *no* useful function whatsoever. under these circumstances, the pending claims do not improperly "engross what may prove to be a broad field." *Brenner*, 383 U.S. at 534-35.

Applicants finally address whether their asserted specific and substantial utility is *credible*. The *Training Materials* define "credible utility" as utility that is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. *Training Materials*, at p. 5 (1999). One of ordinary skill in teh art would appreciate the following facts. First, Applicants teach a novel member of the FGF family. Second, those of ordinary skill in the art, absent Applicants' teaching, *have already* recognized (albeit after Applicants' priority filing date of September 7, 1999) that the polypeptides set forth in SEQ ID NO: 2 and SEQ ID NO: 4 are members of the FGF family of proteins. In particular, Exhibit A illustrates that the human FGF-like polypeptide disclosed in the instant application shares substantial amino acid sequence identity with the FGF polypeptides disclosed by Strausberg (GenBank Accession No. AAH18404, published August 23, 2002) and by

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Nishimura *et al.* (GenBank Accession Nos. BAA99415, published August 3, 2000, Q9NSA1, published October 16, 2001, and NP_061986, published April 6, 2003). Each of these references designates the disclosed human FGF polypeptide as human FGF-21. In addition, Exhibit B illustrates that the murine FGF-like polypeptide disclosed in the instant application shares substantial amino acid sequence identity with the FGF polypeptides disclosed by Strausberg (GenBank Accession No. AAH49592, published April 1, 2003) and by Nishimura *et al.* (GenBank Accession Nos. BAA99416, published July 11, 2000, Q9JJN1, published October 16, 2001, and NP_064397, published June 19, 2003). Each of these references designates the disclosed murine FGF polypeptide as murine FGF-21. The question of what those of ordinary skill in the art would have or could have understood from Applicants' disclosure has been answered by the art: Applicants' claimed nucleic acid encodes an FGF. Third, Applicants explicitly teach that transgenic mice overexpressing FGF-like polypeptide exhibit an abnormal phenotype, one that is described in detail in the specification (page 4, lines 22-28). Applicants contend that those of ordinary skill in the art would find the results of the transgenic mice experiments described in the specification to be credible, these experiments being of a nature that those of ordinary skill in the art routinely perform to determine the function of novel polypeptides. Applicants contend, therefore, that the assertion of a specific and substantial utility is credible to one having ordinary skill in the art.

Applicants contend that because the claims of the instant application are directed to an invention having a specific, substantial, and credible utility, the rejection under 35 U.S.C. § 101 should be withdrawn.

3. Rejections of claims 1(c), 1(d), 2-5, 7-13, and 39-43 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 1(c), 1(d), 2-5, 7-13, 39-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Action, the as-filed specification does not meet the written description requirement for claiming a genus of nucleic acid molecules comprising a nucleotide sequence that hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence set forth in SEQ ID NO: 3 or a nucleotide

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sequence encoding a polypeptide as set forth in SEQ ID NO: 4, wherein expression of the polypeptide encoded by the nucleic acid molecule has an activity of the polypeptide set forth in SEQ ID NO: 4; a region of the nucleotide sequence of SEQ ID NO: 3, encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the polypeptide set forth in SEQ ID NO: 4, or is antigenic; a region of the nucleotide sequence of SEQ ID NO: 3 comprising a fragment of at least about 16 nucleotides; a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 4 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 4; a region of the above nucleotide sequence comprising a fragment of at least about 16 nucleotides; or a nucleotide sequence that is complementary to any of the above nucleotide sequences. Specifically, the Action states that claims 1(c), 1(d), 39, and 40 encompass sequences that are not necessarily SEQ ID NO: 2 or SEQ ID NO: 4, but which must exhibit one of the activities contemplated by the as-filed specification.

The Action states that possession of the claimed invention may be shown by an actual reduction to practice of the invention, a clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. In addition, according to the Action, an adequate written description of the claimed invention requires knowledge in the prior art or a description of the molecular structures of a representative number of species of the claimed genus. The Action states that because the claims require essential or critical elements that are not adequately described in the specification and that were not conventional in the art at the time of filing, and because a skilled artisan cannot envision the detailed structure of a representative number of species of the claimed genus that exhibit the contemplated biological functions, one skilled in the relevant art would not have recognized that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully disagree with the Action's assertion that an adequate written description of the claimed invention *requires* knowledge in the prior art or a description of the molecular structures of a representative number of species of the claimed genus. Applicants note that the *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement* ("*Guidelines*") state that an adequate written description of the claimed

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invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Guidelines,* 66 Fed. Reg. 1099, 1105 (2001). With regard to a claim directed to a genus, the *Guidelines* specifically state that the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice, *or* reduction to drawings, *or* by disclosure of relevant, identifying characteristics (*i.e.,* structure *or* other physical *or* chemical properties, *or* by functional characteristics coupled with a known or disclosed correlation between function and structure, *or* by a combination of such identifying characteristics) sufficient to show the applicant was in possession of the claimed genus. *Guidelines,* 66 Fed. Reg. 1099, 1106 (2001) (*emphasis added*).

With regard to the Action's assertion that the specification does not provide a sufficient description of the genus of nucleic acid molecules encompassed by claims 1(c), 1(d), 39, and 40, Applicants note that claims 1(c), 1(d), 39, and 40 have been amended to recite an isolated nucleic acid molecule comprising a nucleotide sequence that hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3, the nucleotide sequence of the DNA insert in ATCC Deposit No. PTA-626, or a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4, wherein expression of the polypeptide in a transgenic animal results in either a decrease in the animal's body weight, a decrease in animal's liver or spleen weight as a percentage of the animal's body weight, or an increase in the animal's thymus weight as a percentage of the animal's body weight; a region of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3 or the DNA insert in ATCC Deposit No. PTA-626, encoding a polypeptide fragment of at least about 25 amino acid residues; a region of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3 or the DNA insert in ATCC Deposit No. PTA-626 comprising a fragment of at least about 16 nucleotides; a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4 with at least one conservative amino acid substitution, wherein expression of the encoded polypeptide in a transgenic animal results in either a decrease in the animal's body weight, a decrease in animal's liver or spleen weight as a percentage of the animal's body weight, or an increase in the animal's thymus weight as a percentage of the animal's body weight; a region of the above nucleotide sequence comprising a fragment of at least about 16 nucleotides; or a nucleotide sequence that is complementary to any of

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the above nucleotide sequences. Applicants respectfully contend that their amendments overcome the asserted ground of rejection, as the recitation of the functional limitations in the claims, coupled with their explicit disclosure of a phenotype associated with overexpression of the FGF-like polypeptides encoded by the claimed nucleic acids, is sufficient disclosure of relevant, identifying characteristics (*i.e.,* structure *or* other physical *or* chemical properties, *or* by functional characteristics coupled with a known or disclosed correlation between function and structure, *or* by a combination of such identifying characteristics) to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

With regard to the recitation of nucleic acid molecules encoding FGF-like polypeptide fragments, Applicants contend that because the specification explicitly teaches the amino acid sequence for murine and human FGF-like polypeptide (Figures 1 and 2A-2B), the specification inherently discloses fragments of murine and human FGF-like polypeptide, since fragments are merely portions of the specifically disclosed full-length murine and human FGF-like polypeptide sequences. Applicants contend that in view of the explicitly-disclosed sequences provided by the instant application, one of ordinary skill in the art could readily determine the structure of nucleic acid molecules encoding fragments of the polypeptide of SEQ ID NO: 1 or SEQ ID NO: 3 or the polypeptide encoded by the DNA insert of ATCC Deposit No. PTA-626, and would recognize that Applicants were in possession of the claimed invention Applicants, therefore, submit that claims reciting such FGF-like polypeptide fragments satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

With regard to the recitation of nucleic acid molecules encoding conservatively-substituted FGF-like polypeptide variants, Applicants note that the instant application teaches (a) the amino acid sequences for murine and human FGF-like polypeptide (Figure 1 and Figures 2A-2B); (b) that conservative amino acid substitutions may be made in those portions of human FGF-like polypeptide that are not conserved among FGF-like orthologs (page 38, line 29 to page 39, line 6); and (c) rubrics recognized in the art for making conservative amino acid substitutions (Table I; pages 15-16). Applicants provided, in their response to the Office Action mailed September 26, 2001, an exemplary sequence comparison of the disclosed human and murine FGF-like polypeptides, prepared according to the teachings of the instant specification, illustrating those portions of the FGF-like polypeptide that are conserved between these FGF-like orthologs. Applicants contend that

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such sequence analyses were within the skill of one having but ordinary skill in the art at the time the instant application was filed using the teachings in the instant application and knowledge in the art, and note, in fact, that such a sequence comparison was used to identify the species encompassed by the genus defined in new claim 48. Applicants also contend that because the specification explicitly teaches the amino acid sequences for murine and human FGF-like polypeptide and that conservative amino acid substitutions may be made in those portions of human FGF-like polypeptide that are not conserved among FGF-like orthologs, the specification discloses those positions within human FGF-like polypeptide tolerable of conservative substitution (*i.e.*, the specification discloses relevant, identifying characteristics, namely, the structural properties of conservatively substituted human FGF-like variants). Applicants contend that in view of the teachings in the instant application and knowledge in the art at the time the instant application was filed, one of ordinary skill in the art would appreciate structure of nucleic acid molecules encoding conservatively-substituted FGF-like polypeptide variants, and would recognize that Applicants were in possession of the claimed invention. Applicants, therefore, submit that claims reciting such FGF-like polypeptide variants satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

The Office Action also asserts a rejection of claims 1(c), 1(d), 2-5, 7-13, and 39-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Action states that because the as-filed specification does not provide sufficient guidance or support to reasonably enable the broad scope of the claims, the members of the FGF family display a broad range of biological activities, and it is well-recognized in the art that a protein's function cannot be determined from structural similarity *alone*, the specification fails to teach the skilled artisan how to make and use the claimed polypeptides without resorting to undue experimentation to determine the specific biological activities of these polypeptides. In addition, the Action states that the specification provides little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine the positions in the claimed polypeptides that are tolerant to change, and the nature and extent of changes that can be made at these positions.

Specifically, the Action states that because the specification does not disclose or provide evidentiary support for a specific biological activity of the disclosed polypeptides, claim 12, which

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recites a process for determining whether a compound inhibits FGF-like polypeptide activity, is not reasonably enabled. The Action also states that because claims 5 and 42 encompass a process of producing *any* FGF-like polypeptide, these claims are not reasonably enabled. The Action further states that because claims 2 and 9-11 are not limited to cultured or isolated host cells, these claims are not reasonably enabled.

Applicants respectfully disagree with the Action's assertion that the ascribed function of the claimed polypeptides rests *only* on their structural similarity to members of the FGF family, as discussed more fully in section 2 above. Applicants briefly reiterate that their disclosure, at page 4, lines 22-28, that 6-8 week old transgenic mice overexpressing an FGF-like transgene exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, including reduced body weight, reduced liver weight as a percent of body weight, reduced spleen weight as percent of body weight, increased thymic weight as percent of body weight, and poorly developed ovaries with lack of significant follicular development. Applicants contend, therefore, that they have affirmatively supplied a specific biological function for polypeptides encoded by teh claimed nucleic acid molecules, and that the function of the disclosed polypeptides thus rests on *more* than their structural similarity to members of the FGF family.

Applicants also respectfully disagree with the Action's assertion that the specification provides little guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine the positions in the disclosed polypeptides that are tolerant to change, and the nature and extent of changes that can be made at these positions. For example, as described above, the instant specification explicitly teaches both the amino acid sequences for murine and human FGF-like polypeptide and that conservative amino acid substitutions may be made in those portions of the human FGF-like polypeptide that are not conserved among other FGF-like orthologs, and therefore, implicitly teaches those positions within human FGF-like polypeptide that are tolerable of conservative substitution. There is no evidence of record that the metes and bounds of the claimed invention would not be immediately evident to one having ordinary skill in the art through the practice of nothing more than routine experimentation.

Applicants also respectfully disagree with the Action's assertion that one of ordinary skill in the art would have to resort to undue experimentation in order to demonstrate that a particular nucleic acid molecule encoded a polypeptide exhibiting FGF-like properties. Applicants note that

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claims 1 and 40 have been amended to recite an isolated nucleic acid molecule comprising (a) a nucleotide sequence that hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3, the nucleotide sequence of the DNA insert in ATCC Deposit No. PTA-626, or a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4; or (b) a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4 with at least one conservative amino acid substitution; *wherein* expression of the polypeptide encoded by the nucleotide sequence of either (a) or (b) in a transgenic animal results in either a decrease in the animal's body weight, a decrease in animal's liver or spleen weight as a percentage of the animal's body weight, or an increase in the animal's thymus weight as a percentage of the animal's body weight. Applicants contend that, in view of the state of the art at the time the instant application was filed, the amount of experimentation required to demonstrate that a particular polypeptide exhibits specific properties in a transgenic mouse would be analogous to the amount of experimentation required to screen numerous hybridomas in order to identify one that produces a high affinity IgM monoclonal antibody. *In re Wands*, 858 F.2d 731, 740, 8 U.S.P.Q.2d (BNA) 1400, 1407 (Fed. Cir. 1988) (holding that it would not require undue experimentation would to obtain antibodies needed to practice the claimed invention). Moreover, Applicants also disagree with the Action's assertion that the *intended use* of the claimed nucleic acid molecules is for *making* a transgenic mouse. Applicants contend that the intended result of the experiments described at page 4, lines 22-28 of the instant specification is not limited to creation of a transgenic mouse, but rather includes the effects of overexpressing an FGF-like polypeptide ortholog in an animal, *i.e.*, establishing a phenotype associated with the biological function of the polypeptide encoded by the claimed nucleic acid molecules.

Applicants also respectfully disagree with the Action's assertion that claim 12, which recites a process for determining whether a compound inhibits FGF-like polypeptide activity, is not reasonably enabled because the specification does not disclose or provide evidentiary support for a specific biological activity of the disclosed polypeptides. As discussed in section 2 above, the instant application the instant application explicitly teaches that 6-8 week old transgenic mice overexpressing an FGF-like transgene exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, including reduced body weight, reduced liver weight as a percent of body weight, reduced spleen weight as percent of body weight, increased thymic weight as percent of

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body weight, and poorly developed ovaries with lack of significant follicular development (page 4, lines 22-28). Thus, one of ordinary skill in the art would recognize that compounds that inhibit FGF-like peptide activity would antagonize this phenotype. Applicants contend, therefore, that claim 12 satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph.

With regard to the Action's assertion that claims 5 and 42 are not reasonably enabled because they encompass a process of producing *any* FGF-like polypeptide, Applicants note that claims 5 and 42 have been amended to recite "[a] process of producing a polypeptide encoded by the nucleic acid molecule of any of Claims 1, 39, 40, or 48". Applicants do not understand that the Patent Office has taken the position that previously presented claims 1, 39, or 40 recite *any* FGF-like polypeptide, particularly because to do so would require that all recited limitations in those claims except the phrase "FGF-like polypeptide" be ignored. Applicants contend that claims 5 and 42, as amended, do not encompass a process of producing *any* FGF-like polypeptide, and therefore, that these claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

With regard to the Action's assertion that claims 2 and 9-11 are not reasonably enabled because claims 2 and 9 are not limited to cultured or isolated host cells, Applicants note that claim 2, as previously presented, recites "[a] recombinant host cell" and that claim 9 has been amended to recite "[a] recombinant host cell." Applicants contend that this term is understood in the art to include the property that the cell is isolated (typically, in cell culture), in contrast to "transgenic," which is understood in the art to mean a cell or an organism (or the organism comprising said cells) that has been transformed with an exogenous nucleic acid. Applicants thus contend that because claims 2 and 9 recite *recombinant* host cells, these claims do not encompass non-isolated cells, and therefore, that these claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

Applicants contend that, in view of the teachings in the instant application and knowledge in the art at the time the instant application was filed, the as-filed specification enables the scope of the pending claims by teaching the skilled artisan how to make and use nucleic acid molecules encoding FGF-like polypeptides and FGF-like polypeptide fragments, without resorting to undue experimentation. Applicants, therefore, submit that the claims of the instant application satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, first paragraph,

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have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

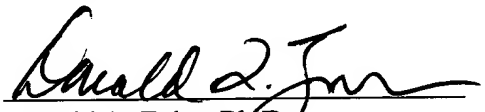
CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Nguyen believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: October 8, 2003

By: 
Donald L. Zuhn, Ph.D.
Reg. No. 48,710

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Chicago, Illinois 60606
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EXHIBIT A

```
ClustalW (v1.4) multiple sequence alignment

5 Sequences Aligned              Alignment Score = 13466
Gaps Inserted = 0                Conserved Identities = 208

Pairwise Alignment Mode: Slow
Pairwise Alignment Parameters:
    Open Gap Penalty = 10.0    Extend Gap Penalty = 0.1
    Similarity Matrix: blosum

Multiple Alignment Parameters:
    Open Gap Penalty = 10.0    Extend Gap Penalty = 0.1
    Delay Divergent = 40%      Gap Distance = 8
    Similarity Matrix: blosum

Processing time: 2.0 seconds


huFGF-like     1 MDSDETGFEHSGLWVSVLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYLY  50
AAH18404       1 MDSDETGFEHSGLWVSVLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYLY  50
BAA99415       1 MDSDETGFEHSGLWVSVLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYLY  50
NP_061986      1 MDSDETGFEHSGLWVSVLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYLY  50
Q9NSA1         1 MDSDETGFEHSGLWVSVLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYLY  50
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huFGF-like    51 TDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSR 100
AAH18404      51 TDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSR 100
BAA99415      51 TDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSR 100
NP_061986     51 TDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSR 100
Q9NSA1        51 TDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSR 100
                 **************************************************

huFGF-like   101 FLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK 150
AAH18404     101 FLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK 150
BAA99415     101 FLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK 150
NP_061986    101 FLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK 150
Q9NSA1       101 FLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK 150
                 **************************************************

huFGF-like   151 SPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPS 200
AAH18404     151 SPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPS 200
BAA99415     151 SPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPS 200
NP_061986    151 SPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPS 200
Q9NSA1       151 SPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPS 200
                 ********************** ************************** 

huFGF-like   201 QGRSPSYAS 209
AAH18404     201 QGRSPSYAS 209
BAA99415     201 QGRSPSYAS 209
NP_061986    201 QGRSPSYAS 209
Q9NSA1       201 QGRSPSYAS 209
                 *********
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EXHIBIT B

```
ClustalW (v1.4) multiple sequence alignment

5 Sequences Aligned              Alignment Score = 13570
Gaps Inserted = 0                Conserved Identities = 210

Pairwise Alignment Mode: Slow
Pairwise Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.1
    Similarity Matrix: blosum

Multiple Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 0.1
    Delay Divergent = 40%     Gap Distance = 8
    Similarity Matrix: blosum

Processing time: 1.7 seconds


muFGF-like      1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL  50
AAH49592        1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL  50
BAA99416        1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL  50
NP_064397       1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL  50
Q9JJN1          1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL  50
                  **************************************************

muFGF-like     51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100
AAH49592       51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100
BAA99416       51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100
NP_064397      51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100
Q9JJN1         51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100
                  **************************************************

muFGF-like    101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150
AAH49592      101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150
BAA99416      101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150
NP_064397     101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150
Q9JJN1        101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150
                  **************************************************

muFGF-like    151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200
AAH49592      151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200
BAA99416      151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200
NP_064397     151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200
Q9JJN1        151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200
                  **************************************************

muFGF-like    201 LQGRSPSYAS 210
AAH49592      201 LQGRSPSYAS 210
BAA99416      201 LQGRSPSYAS 210
NP_064397     201 LQGRSPSYAS 210
Q9JJN1        201 LQGRSPSYAS 210
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